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Unipolar Relatives in Bipolar Pedigrees: A Search for Elusive Indicators of Underlying Bipolarity

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In an effort to identify features indicative of underlying bipolarity within the unipolar relatives of bipolar probands, we compared unipolar relatives of bipolars with unipolar relatives of controls. Using data from the Yale-NIMH Collaborative Study of Depression, we compared a number of demographic and clinical features individually, and then developed a logistic regression model for the differences found. Unipolar relatives of bipolars were generally similar to relatives of controls, but they were older and more likely to suffer from more severe, even psychotic, depression, and somewhat less likely to report a brief transition into their illness. A multiple logistic regression model for observed differences was highly statistically significant, but had limited ability to discriminate effectively between the two groups. These findings suggest that more stringent diagnostic criteria might be beneficial if unipolar relatives are counted as affected in linkage studies of bipolar disorder. The ability of this strategy to improve the "clinical phenotype" is limited, however, and other approaches may be needed to identify features of underlying bipolarity and thus to define "caseness" for unipolar relatives in linkage analyses of bipolar disorder. © 1996 Wiley-Liss, Inc.

KEY WORDS: bipolar disorder, major depression, linkage analysis, caseness index, phenotype

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INTRODUCTION

Despite substantial genetic epidemiologic evidence that genetic factors play a major role in the etiology of bipolar disorder (BP), linkage analysis of this disorder has been plagued by ambiguous and inconsistent findings [Egeland et al., 1987; Baron et al., 1987, 1993; Kelsoe et al., 1989; Faraone et al., 1990]. These difficulties may result from the absence of a single major locus segregating for the disorder or from a number of other possible causes [Baron et al., 1990a; Risch, 1990; Plomin, 1990; Spence et al., 1993; Gelernter, 1995]. However, difficulties specifying the affected phenotype might well obscure the presence of a major locus [Baron et al., 1990*b*; Martinez et al., 1989; Suarez et al., 1990; Gruis et al., 1993; Faraone et al., 1995a]. And nowhere are these difficulties more pressing than for the more numerous and etiologically heterogeneous unipolar (UP) relatives: should they or should they not be considered affected?

In an effort to address this question, a conceptual model, described in detail elsewhere [Blacker and Tsuang, 1993], was developed. In brief, it is argued that some UP relatives of BP probands, who can be viewed as "potential BPs," i.e., UP individuals who will or might (from the standpoint of genetic liability) go on to manifest BP, must be present because they are related to the BP proband. However, there must be others, the "generic UPs," i.e., individuals representative of UP in the population at large, who are present in such pedigrees simply by chance. These groups are not directly observable. However, based on overall BP-UP differences [Goodwin and Jamison, 1990; Winokur et al., 1993], on clinical data about the features of depression in BP individuals [Coryell et al., 1984; Beigel and Murphy, 1971; Goodwin and Jamison, 1990], on follow-up data about switching from UP to BP illness [Winokur and Wesner, 1987; Akiskal et al., 1983, 1995], on family studies of major depression [Weissman et al., 1984a,b], and on the known underreporting of manic symptomatology [Goodwin and Jamison, 1990], we hypothesized that potential BPs would be younger and more often

male; would have earlier onset and more severe and frequent episodes; and would manifest more reverse neurovegetative signs, psychotic features, difficulties with self-esteem and concentration, and subthreshold bipolar features. In addition, based on clinical and family comorbidity data, we would expect to observe more alcohol abuse [Regier et al., 1990; Reich et al., 1974] and less panic disorder [Maser and Cloninger, 1990] in the potential BPs.

Given this conceptual model, analogous but diluted differences should be seen between UP relatives of BPs (among whom there should be many potential BPs), and UP relatives of UPs or controls (among whom generic UPs should predominate). Thus, a logistic regression model for the differences between the two groups could be used to construct a "potential bipolarity" scale. This scale could then serve as a form of caseness index [Ott, 1990, 1991; Terwilliger and Ott, 1994] for weighting UP relatives in linkage studies of BP disorder, analogous to the stability index proposed by Rice et al. [1987a] and Baron et al. [1990b]. While individual traits such as male gender, early onset, or severe symptoms would not be expected to be highly predictive of potential bipolarity, a set of traits taken together might achieve fair discrimination between groups.

In a sense, this is an extension of the methods used earlier by Gershon et al. [1986], who began with two groups of ill relatives (relatives of affectively ill patients and relatives of controls) meeting minimal diagnostic criteria, and found that the more stringent modified Research Diagnostic Criteria (RDC) [Mazure and Gershon, 1979] maximized the discrimination between these groups. This study also found that incapacitation in social role and recurrence were both more common in ill relatives of patients than in ill relatives of controls. In the present case the method focuses specifically on depressed relatives of *bipolar* probands in comparison to depressed relatives of controls, and on attempts to summarize the differences between groups in a single measure of how likely a given relative is to have an underlying bipolar genotype.

In earlier work [Blacker et al., 1993], we reported on a comparison of UP relatives of BPs with UP relatives of UPs from the Collaborative Study of the Psychobiology of Depression [Katz and Klerman, 1979; Rice et al., 1989; Andreasen et al., 1987], showing predicted differences in sex ratio and subsyndromal bipolar features, but no differences in age at onset, duration or frequency of episodes, or comorbid conditions, and showing on average milder depressive episodes in UP relatives of BPs by several measures. We hypothesized that the discrepancy between the predicted and observed differences might result from using the UP relatives of *unipolar* probands as a comparison group, since they have been shown to have a more severe form of depressive illness [Weissman et al., 1986; Gershon et al., 1986; Kendler et al., 1994]. We report here on a comparison of UP relatives of BP probands with UP relatives of control probands from the Yale-NIMH Collaborative Study of Depression [Weissman et al., 1982, 1984c; Gershon et al., 1982, 1986].

MATERIALS AND METHODS

Sample

The Yale-NIMH Collaborative Study of Depression was a large family study which included a total of approximately 487 probands and 2,485 of their relatives ascertained at two sites and evaluated following a common protocol [Weissman et al., 1982, 1984c; Gershon et al., 1982]. Probands were administered a modified Schedule for Affective Disorders and Schizophrenia (SADS) [Endicott and Spitzer, 1978], and relatives were interviewed with a modified SADS Lifetime version (SADS-L) [Endicott and Spitzer, 1978]. In the original study, both probands and relatives were diagnosed according to modified RDC criteria [Spitzer et al., 1978; Mazure and Gershon, 1979], following a best-estimate procedure using all available information from diagnostic interviews, family history, and medical records. The analyses presented here utilize subjects selected from among first-degree relatives based on their diagnosis and those of their probands.

Proband diagnosis. For purposes of this analysis, BP probands were those with a best-estimate RDC diagnosis of manic disorder, bipolar-I disorder (major depression plus mania), or schizoaffective mania, mainly affective subtype (SAMA). SAMA was included along with manic and bipolar-I (BP-I) disorders in order to approximate the DSM-III [American Psychiatric Association, 1980], DSM-IIIR [American Psychiatric Association, 1987], and DSM-IV [American Psychiatric Association, 1994] criteria for bipolar-I disorder. The broader tolerance of psychosis during manic episodes in DSM-III, -IIIR, and -IV was based on several studies showing RDC SAMA to be virtually indistinguishable from RDC BP-I disorder in prognosis, treatment response, and family history of affective disorders [Andreasen et al., 1987; Pope et al., 1980]. Relatives of bipolar-II (BP-II) probands were not included because this disorder bears an unclear relationship to bipolar-I disorder [Endicott et al., 1985; Kupfer et al., 1988; Akiskal et al., 1995], and maximum separation between groups was desired. Using DSM-III criteria, there were 101 BP probands (all from the NIMH site), with 400 interviewed first-degree relatives available. There were 125 control probands (82 from Yale and 46 from NIMH), with 258 *interviewed* first-degree relatives available. The number of available probands and relatives may differ somewhat from published reports because 1) we included relatives of SAMA probands with those of bipolar-I probands, 2) in keeping with current practice, we included relatives of black probands from the NIMH who were excluded from some reports, 3) we included relatives of medically ill control probands from the NIMH who were excluded from some reports, and 4) we restricted these analyses to *interviewed* first-degree relatives, using only those cases for which the requisite SADS-L interview data were available.

Diagnosis in relatives. Although the original methods of data collection and diagnosis were standardized across the two sites, and the data were analyzed together in several published reports [e.g., Weissman et al., 1984c; Gershon et al., 1986], a combined data set no longer exists. Instead, because the data

from each site were stored and used separately for over 10 years, currently available diagnostic indicators are not strictly parallel at the two sites. In particular, these indicators differ in the range of diagnostic criteria, diagnostic hierarchies, and sources of information used to arrive at diagnoses. In order to obtain strictly parallel diagnoses at the two sites using currently available data, diagnoses in relatives for the present study were made by computer algorithm using the SADS-L interview data alone. Thus, only first-degree relatives on whom a SADS-L interview was available were considered.

Among the diagnostic criteria in use in family and linkage studies, the relatively less stringent RDC criteria were chosen to define the sample for these analyses because they allowed for a broad range of depressive symptomatology and severity. A broad range of depressed individuals was desirable in order to array depressed relatives along a scale of potential bipolarity.

Relatives were included if they met RDC criteria [Spitzer et al., 1978] for major depression (MDD), and if they had no history of schizophrenia, mania, or hypomania. No other exclusions were employed. Following this procedure, there were 55 relatives of BPs with MDD, and 40 relatives of controls with MDD.

In order to validate the diagnostic procedures and assess the overall quality of our data management, we compared our SADS-L diagnosis to the available diagnostic indicators from each site for all of the 400 relatives of BPs and 258 relatives of controls. For the Yale sample, the standard for MDD was a best-estimate diagnosis of probable or definite MDD by the modified RDC criteria used in the original Yale-NIMH Collaborative Study [Mazure and Gershon, 1979], or by RDC or DSM-III criteria (which were available for this site only), with no RDC diagnosis of probable or definite hypomania, mania, or schizophrenia. For the NIMH sample, the standard for MDD was an interview or best-estimate diagnosis of MDD by the modified RDC criteria [Mazure and Gershon, 1979] used in the original Yale-NIMH Collaborative Study. Because these diagnostic indicators from the originating sites were based on different information (e.g., SADS-L interview plus family history and hospital records, and not just SADS-L data alone), and often followed different diagnostic criteria, they were not expected to correspond precisely to our diagnoses. Nonetheless, they provided an outside standard against which we could check the validity of our diagnostic algorithms and the data on which they were based.

These analyses showed the overall rates of agreement to be good for both sites, and the vast majority of the disagreements were with related diagnoses. For Yale, there was agreement on 17 cases of MDD among 137 relatives. There were 5 false-positives (i.e., our computer algorithm diagnosed MDD and the site's diagnostic indicators did not): 3 with minor depression according to the Yale indicators, 1 with depressive personality and bereavement, and 1 with bereavement. There were 4 false-negatives: 3 who answered "no" to the gate questions for depression and thus had no SADS-L data on depressive symptoms, and 1 who had bipolar-II disorder by our criteria but had only *possible* hypomania according to Yale and was thus considered to have MDD. For the NIMH, the false-positive rate was higher because only diagnoses based on the stringent modified RDC criteria used in the original Collaborative Study [Mazure and Gershon, 1979] were available in the data base. There was agreement on 42 cases of MDD among 523 relatives. There were 33 false-positives, of whom 25 had an NIMH diagnosis of minor depression, 2 of depressive personality, 2 of bereavement, 2 of schizoaffective depression, 1 of bipolar-I (with no SADS-L data on mania available), and 1 of cyclothymia. There were 4 false-negatives, 2 who answered "no" to the gate question for depression and thus had no data on depressive symptoms, 1 just under the symptom-number threshold for diagnosis of MDD according to the SADS-L, and 1 with bipolar-II disorder by our criteria but with a diagnosis of MDD plus hyperthymia from the NIMH, and thus still considered to have MDD.

Statistical Analysis

Univariate comparisons. For most categorical variables, we report the results of chi-square tests. For those categorical variables with expected counts of 5 or fewer in one or more cells, we report the results of Fisher's exact test. For approximately normal continuous or ordinal variables we report the results of two sample t-tests. For continuous or ordinal variables with skewed distributions, we report the results of Wilcoxon tests for two independent samples.

Because our primary aim is the separation of the groups, rather than hypothesis testing, P values for these tests are reported primarily for informational or screening purposes, and Bonferroni corrections are not used. The critical issue for our purposes is the size of the differences and not their statistical reliability.

In addition, P values must be interpreted with caution in this setting. For the sake of simplicity, we chose to ignore clustering of individuals within families. If this clustering is not taken into account, shared variance within families would lead to an underestimate of true variance, and therefore an overestimate of statistical significance. The magnitude of this problem should not be large, because the size of the families is not extreme, i.e., approximately 54% of individuals come from families contributing only one individual, 77% from families contributing one or two, and 96% from families contributing three or fewer. Should the method prove sufficiently promising, however, appropriate corrections would need to be made for possible covariance within families.

Multivariate analysis. Logistic regression was performed with the SAS Statistical Package [SAS Institute, 1989], beginning with all variables with potential to discriminate between the groups, and using a process of backward elimination. Differences between models were evaluated using the change in likelihood ratio. However, since the aim of the modelling was to achieve as much explanatory power as possible, strict cutoffs for statistical significance were not used. Critical ratio (Z) statistics for regression coefficients are reported primarily for informational purposes. As in the

univariate setting, because of expected correlations within families, standard errors are underestimated. However, the predicted probabilities depend on consistent estimates of the regression coefficients, not of their standard errors, so correlations within families should not affect our results.

Because the critical issue is the difference in fitted probabilities between the groups, we present it in three ways. First, to give an intuitive feel for the predictive abilities of the model, we identify individuals with the maximum and minimum fitted probabilities under the model and look to see whether the model predicts their group of origin. Second, to examine the matter graphically, we present side-by-side boxplots [Emerson and Strenio, 1983] of the fitted logits for each group. The logit is the natural log of the odds (probability over 1 minus probability). The box contains half of the distribution (from the first through the third quartile), with a line drawn at the median and a plus sign indicating the mean. The whiskers extend up to 1.5 times the interquartile range, and asterisks indicate any outliers beyond this range. Third, to examine the separation analytically, we use the reduction in the likelihood equivalent error rate (LEER) [DuMouchel and Waternaux, 1983] of the null model (which is based on prior probability of the outcome of interest) by the full model (based on fitted probability). This basically describes the fraction of the error in the null model that is explained by the full model, and is thus analogous to R^2 in ordinary least squares regression. Of course, the real test of the approach discussed here would be its ability to improve the power of a linkage analysis.

RESULTS

Table I compares the demographic features of all relatives of BP and control probands, and the observed rates of major depression in each sample. There are no significant differences in age and sex ratio between the two groups. Rates of depression are also remarkably similar in both groups, and higher overall than has been reported in this data set [Weissman et al., 1984c; Gershon et al., 1982]. This is almost certainly due to the use in the present study of the less stringent RDC criteria [Spitzer et al., 1978] rather than the *modified* RDC criteria used by the original investigators [Mazure and Gershon, 1979], which require a longer duration and evidence of impairment in the principal social role. When we apply the modified RDC criteria in the present study, the prevalence of MDD is 6.6% (17/258) in relatives of controls, and 9.5% (38/400) in relatives of BPs. These numbers are remarkably similar to those reported in the original published report [Weissman et al., 1984c: 5.6% in relatives of controls, and 9.5% in relatives of BPs]; the small discrepancies are probably due to differences in the sample and data used as noted above. The greater difference in prevalence of depression between relatives of controls and relatives of BPs when the more stringent diagnostic criteria are employed is consistent with the findings of the original investigators that more stringent diagnostic criteria resulted in more marked familial aggregation [Gershon et al., 1986].

Univariate Comparisons

Demographics. Comparison of demographic features appears in Table II. There was no significant difference in sex ratio, but UP relatives of BPs are significantly older than UP relatives of controls.

Characteristics of depression. Comparison of features of depression is shown in Table III. Up relatives of BPs show a significantly later age-of-onset, more psychotic features, and increased incapacitation when compared to UP relatives of controls. UP relatives of BPs are also more likely to meet the more stringent modified RDC criteria [Mazure and Gershon, 1979]. In addition, given the relatively small sample size, it is worth noting that UP relatives of BPs were more likely to report recurrent disease and psychomotor retardation, and UP relatives of controls were more likely to report irritability and rapid onset (from normal to depressed within 48 hr).

Subsyndromal bipolarity. Comparisons for subsyndromal bipolar features are shown in Table IV. Manic symptomatology of any kind was extremely rare. However, UP relatives of controls were more likely to report periods of euphoria just before and after their depressive episodes.

Comorbidity. Comparison for comorbidity is shown in Table V. These analyses used relatively inclusive screening questions for these comorbid disorders, and found no differences in a positive screen for alcoholism, panic disorder, or dysthymia between the two groups.

Regression Analysis

The final regression model is described in Table VI. Except for 1) age and age-at-onset and 2) incapacitation and meeting modified RDC criteria (which requires either incapacitation or impairment) [Mazure and Gershon, 1979], there was little colinearity among the variables, so most of the major effects did not depend substantially on the presence of other variables in the model.

TABLE I. Characteristics of Source Populations*

Variable	Measure	Relatives of BPs	Relatives of controls	*P*	Test
Size	n	400	258		
Sex	% (n) male	48.5 (194)	45.3 (117)	.43	X
Age	m (SD)	41.8 (18.8)	40.6 (17.9)	.40	T
MDD	% (n)	13.8 (55)	15.5 (40)	.52	X

*m (SD), mean (SD); X, chi-square test; T, t-test.

TABLE II. Demographics*

Variable	Measure	UP relatives of BPs	UP relatives of controls	P	Test
Size	n	55	40		
Sex	% (n) male	42.6 (23)	50.0 (20)	.43	X
Age	m (SD)	44.9 (17.1)	34.8 (12.9)	.002	T

*m(SD), mean (SD); X, chi-square test; T, t-test.

The 5 individuals with the maximum fitted probabilities according to the model are all among the relatives of BPs. A review of their diagnostic indicators from the originating sites reveals four cases of MDD and one with a best-estimate diagnosis of bipolar-II (whose SADS-L interview, however, showed no evidence of hypomania, making his interview-based diagnosis from the site MDD). Of the 5 individuals with the minimum fitted probabilities according to the model, all were among UP relatives of controls, 4 from Yale and 1 from the NIMH. A review of their diagnostic indicators from the originating sites reveals two cases of MDD, two cases of minor depression, and one of bereavement.

The model is somewhat limited in its ability to discriminate between groups, as the boxplots of the fitted logits (Fig. 1) demonstrate. The reduction in LEER, shown in Table VI for this model, is consistent with this limited discriminatory ability. The LEER for the full model is 0.22, and that for the corresponding null model is 0.42, a 45% reduction.

Alternative Analysis

Because these results differed so much from the comparison of UP relatives of BPs with UP relatives of *UP probands* reported earlier [Blacker et al., 1993], the same comparison was repeated in the Yale-NIMH data set. There was a total of 163 UP probands, 89 mild (all from Yale) and 74 severe (i.e., hospitalized for 5 days or more; 30 from NIMH and 44 from Yale). Of the 364 interviewed relatives of UP probands available, 92 met RDC criteria for MDD according to their SADS-L interview data, and were compared in these analyses with the 55 UP relatives of BPs presented above.

On the whole, UP relatives of BP and UP probands were fairly similar on these measures; the data are not presented in detail here. UP relatives of BPs had a greater chance of reporting incapacitation, and a trend for reporting more psychotic features and less irritability than relatives of UPs. In addition, in this fairly small sample, it is worth noting that UP relatives of BPs included more males; had slightly later age-at-onset; had slightly fewer symptoms; and had a smaller tendency to report >3 episodes, rapid onset, increased sleep, or "highs" before or after their depression. UP relatives of BPs were also nonsignificantly less likely to report panic attacks. In keeping with these overall smaller differences than the comparison of UP relatives of BPs vs. UP relatives of controls, the regression model for this alternative analysis had quite limited ability to discriminate between groups. Table VII summarizes these results qualitatively beside the earlier comparison [Blacker et al., 1993] of UP relatives of UPs and BPs.

DISCUSSION

UP relatives of control probands and UP relatives of BP probands were relatively similar across the spectrum of measures examined here, but they did show

TABLE III. Characteristics of Depression

Variable	Measure	UP relatives of BPs (n = 55)[a]	UP relatives of controls (n = 40)[a]	P	Test[b]
Age-at-onset	m (SD)[b]	31.8 (14.6)	25.5 (11.5)	.02	T
≥3 episodes	% (n)[a]	23.6 (12)	15.0 (6)	.33	X
Duration (weeks)	5 # sum[c]	2 4 12 30 156[d]	1 4 12 27 999[d]	.55	W
Number of symptoms	m (SD)	5.49 (1.85)	5.33 (1.58)	.64	T
Incapacitated	% (n)[a]	40.7 (22)	17.5 (7)	.02	X
Rapid onset	% (n)[a]	15.9 (7)	32.5 (13)	.08	X
Irritable	% (n)[a]	52.7 (29)	67.5 (27)	.15	X
Psychotic	% (n)[a]	20.0 (11)	5.0 (2)	.04	F
Decreased concentration	% (n)[a]	71.6 (38)	74.4 (29)	.78	X
Guilt	% (n)[a]	62.3 (33)	62.5 (25)	.98	X
Retarded features	% (n)[a]	48.1 (26)	35.9 (14)	.24	X
Increased sleep	% (n)[a]	23.1 (12)	22.5 (9)	.95	X
Treatment	% (n)[a]	50.0 (27)	37.5 (15)	.23	X
Modified RDC criteria[e]	% (n)[a]	69.0 (38)	42.5 (17)	.01	X

[a]Because of missing data, the denominator for some characteristics is smaller than the reported sample size.
[b]m (SD), mean (SD); X, chi-square test; T, t-test; W, Wilcoxon test; F, Fisher's exact test.
[c]Minimum, 25th percentile; median, 75th percentile; maximum.
[d]999 denotes duration beyond 20 years.
[e]Mazure and Gershon [1979].

TABLE IV. Subthreshold Bipolar Features

Variable	Measure	UP relatives of BPs (n = 55)[a]	UP relatives of controls (n = 40)[a]	*P*	Test[b]
Mania screen	% (n)[a]	3.6 (2)	2.5 (1)	1.0	F
"Highs" pre/post	% (n)[a]	5.8 (3)	15.0 (6)	.17	F

[a]Because of missing data, the denominator for some characteristics is smaller than the reported sample size.
[b]F, Fisher's exact test.

two differences that held up in the multivariate setting as well. As would have been expected based on the earlier work in these data discussed above [Gershon et al., 1986], UP relatives of BPs manifested more severe depression as measured by meeting the more stringent modified RDC criteria [Mazure and Gershon, 1979], and by reporting incapacitation during their depressive episodes. They also showed higher rates of psychotic depression, consistent with earlier findings [Weissman et al., 1984a,b]. In addition, there were nonsignificant differences in the expected direction between the two groups for recurrence and retarded features, both of which were more common among UP relatives of BPs. On the other hand, contrary to expectations, UP relatives of BPs were significantly older and showed later age-at-onset than UP relatives of controls; showed a trend to less rapid onset; and showed nonsignificant increases in the percentage who were male, in irritability, and in "high" periods associated with their depressions.

These findings must be understood in light of the limitations of the study. One of these is the small sample size, which had limited ability to detect modest differences between groups. In addition, there is a possible source of bias because all of the BP families were ascertained at NIMH, while the control families came from both sites. To check for systematic differences by site, we compared the two sites within each of two groups that should have been very similar: UP relatives of control probands, and UP relatives of severe MDD probands. These two groups of depressed relatives were chosen because they were ascertained via probands who were strictly similar at the two sites. Site comparisons within each of the two groups disclosed few significant differences at $P = 0.1$. However, there are three differences that are consistent by site across both proband groups. The first is age, which is consistently (but not significantly) higher at the NIMH than at Yale. The second is age-of-onset, which is consistently later at the NIMH (although the between-site difference is significant only for UP relatives of controls). The third is "highs" before or after depression, which is endorsed by none of the UP relatives of severe UP or control probands from NIMH, but appears in 10% of UP relatives of severe UPs from Yale and 30% of UP relatives of controls from Yale. It is possible that these site differences account for the observed differences in these variables. On the other hand, age, and to an extent age-of-onset, may be less of a concern because (as shown in Table I) there was essentially no difference in age between relatives of controls as a group (from both sites) and relatives of BPs as a group (all of whom were from the NIMH, as noted above).

Implications for the Model

These results are substantially at odds with the phenotypic model proposed earlier [Blacker and Tsuang, 1993] concerning the likely characteristics of UP relatives of BP probands, and thus constitute a negative test of that model. Although the small sample size and the limitations of the diagnostic procedures are such that the present study cannot definitively invalidate the earlier model, these negative findings suggest that other strategies should be sought to optimize the treatment of UP relatives in BP linkage studies. First, a search for differences between UP relatives of BPs and more typical UPs might best focus not on major demographic and clinical features, but instead, perhaps, on other, less often measured, attributes such as temperament [Akiskal et al., 1995], neuropsychological functioning [Faraone et al., 1995b], or specific symptoms [Dubay et al., 1993]. Second, it might be helpful to try other analytic methods such as factor analysis, as was recently used by Baer [1994] to look for differences between obsessive-compulsive disorder related and not related to Tourette syndrome. Third, it appears that a different model might better explain the observed differences between UP and BP. For instance, the differences between UPs and BPs and between UP and BP depression might reflect risk factors for mania given an overall propensity to affective disorder, analogous to the differential risk of obsessive-compulsive disorder and Tourette syndrome within the same family [Pauls et al., 1986]. Consistent with this are the recent data from McMahon et al. [1994] concerning differences in

TABLE V. Comorbidity

Variable	Measure	UP relatives of BPs (n = 55)[a]	UP relatives of controls (n = 40)[a]	*P*	Test[b]
Alcoholism screen	% (n)[a]	25.0 (9)	32.4 (12)	.48	X
Panic attacks	% (n)[a]	15.0 (6)	13.0 (6)	.79	X
Dysthymia screen	% (n)[a]	27.6 (8)	30.0 (12)	.83	X

[a]Because of missing data, the denominator for some characteristics is smaller than the reported sample size.
[b]X, chi-square test.

TABLE VI. Logistic Regression Model: Prediction of Odds of Being Among UP Relatives of BPs vs. UP Relatives of Controls*

Variable	Odds ratio	Coefficient	SE (coefficient)	Z
Intercept		−0.718	0.796	−0.90
Age	1.03	0.027	0.016	1.64
Modified RDC criteria[a]	2.44	0.890	0.485	1.84
Psychotic	7.68	2.038	0.964	2.11
Irritable	0.46	−0.767	0.498	−1.54
Rapid onset	0.28	−1.264	0.645	−1.96

*Model summary: change in deviance, null model vs. full model, 22.5; degrees of freedom, 5; $P = .0004$. Likelihood equivalent error rate of full model, 0.233; error rate of null model, 0.421; reduction, 44.5%.
[a]Mazure and Gershon [1979].

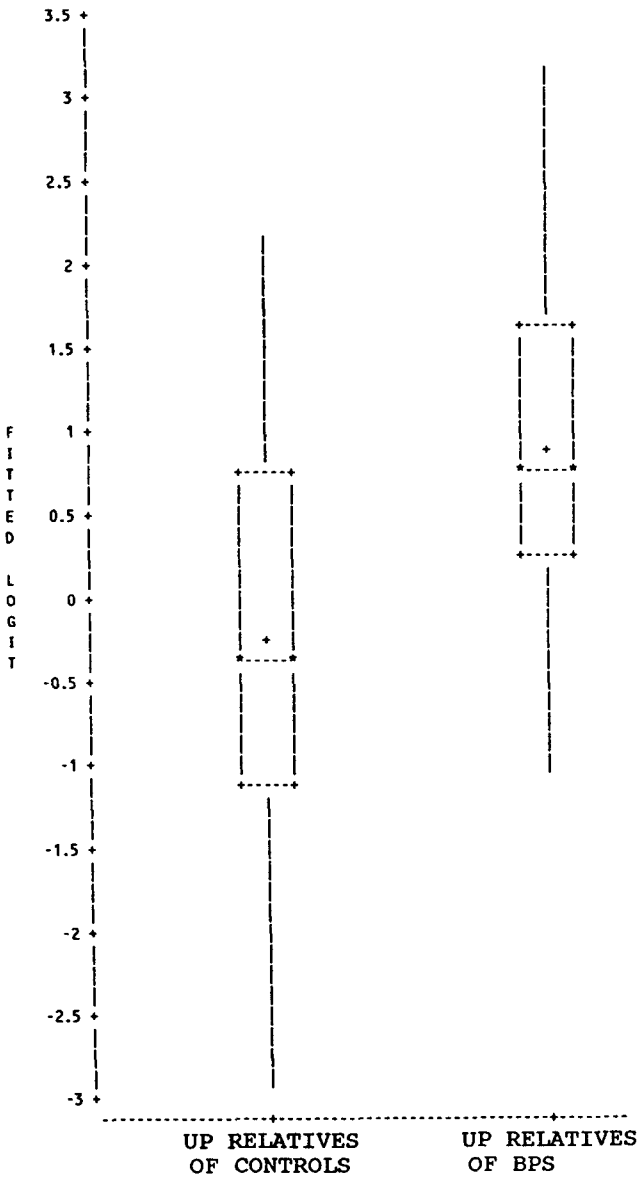

Fig. 1. Fitted logits. See explanation in Materials and Methods under "Multivariate analysis."

age-of-onset of UP and BP relatives within BP families systematically ascertained for a linkage study.

Implications for Genetic Studies

Independent of the causal model, these findings suggest some changes that might improve the definition of the clinical phenotype for BP disorder. First, if UP relatives are to be considered affected in linkage studies of bipolar disorder, it might be preferable to require that they meet modified RDC criteria rather than the less stringent RDC or DSM criteria for depression. This narrower disease definition may have contributed to the chromosome 18 linkage findings of Berrettini et al., [1994], whose possible replication was recently reported [Stine et al., 1995]. Unfortunately, a change to these narrower criteria for MDD could only provide modest increases in specificity. For instance, in this sample, UP relatives of controls, who are likely to represent "sporadic" UP illness, included 42.5% (17/40) who met the more stringent modified RDC criteria for MDD. Perhaps a more specific requirement would be to include only individuals with *psychotic* depression, but this phenomenon is so rare that specificity would be improved at the cost of an enormous loss of sensitivity. A still more specific requirement would be to omit the depressed relatives altogether, and focus only on bipolar relatives, an approach which has received support from a number of segregation studies [Rice et al., 1987b; Pauls et al., 1995; Spence et al., 1995]. However, this approach fails to take advantage of a large amount of potential information among the more numerous depressed relatives.

Even with one or more of these alternative strategies, the status of depressed relatives in bipolar pedigrees remains problematic, and there will necessarily be large numbers of false-positives from the genetic point of view if all such relatives are counted as affected, and large numbers of false-negatives if all are counted as affected, and large numbers of false-negatives if all are counted as unaffected. Of course, it is still possible to use multiple definitions of affected phenotype, but this has been shown to increase the probability of false-positive linkage results [Weeks et al., 1990]. Of note, recent work on Tourette syndrome and its related phenotypes suggests that the use of multiple phenotype

TABLE VII. Comparison of Findings: Yale-NIMH Study* vs. Collaborative Depression Study†

Variable	Yale-NIMH study (UP relatives of BPs vs. UP relatives of UPs)	Collaborative depression study (UP relatives of BPs vs. UP relatives of UPs)
Demographics		
Sex	No significant difference	More males in relatives of BPs (trend)
Age	No significant difference	No significant difference
Characteristics of depression		
Age-at-onset	No significant difference	No significant difference
≥3 episodes	No significant difference	No significant difference
Duration of episodes	No significant difference	No significant difference
No. of symptoms	No significant difference	Lower in relatives of BPs
Incapacitated	More common in relatives of BPs	No significant difference
Rapid onset	No significant difference	Unavailable
Irritable	Less common in relatives of BPs (trend)	Unavailable
Psychotic features	More common in relatives of BPs (trend)	No significant difference
Decreased concentration	No significant difference	Unavailable
Guilt	No difference	Unavailable
Retardation	No significant difference	Unavailable
Increased sleep	No significant difference	Unavailable
Treatment	No significant difference	Less common in relatives of BPs
Modified RDC criteria[a]	No significant difference	Not available
Subsyndromal bipolarity		
Mania screen	No significant difference	More common in relatives of BPs
"Highs" before or after depression	No significant difference	Unavailable
Cheerful energetic traits	Unavailable	More common in relatives of BPs
Comorbidity		
Dysthymia screen	No significant difference	Unavailable
Panic attacks	No significant difference	Less common in relatives of BPs
Alcoholism screen	No significant difference	No significant difference

*Weissman et al. [1982, 1984c], Gershon et al. [1982, 1986].
†Katz and Klerman [1979], Rice et al. [1989], Andreasen et al. [1987].
[a]Mazure and Gershon [1979].

definitions, coupled with a Bonferroni correction for multiple comparisons, might provide more power than limiting the disease definition to the rare core phenotype [Heutink et al., 1995].

Without a definite *best* phenotypic definition, and given the loss of power associated with using multiple definitions, an accurate "caseness" index [Ott, 1990, 1993; Terwilliger and Ott, 1994] or other pseudoquantitative method [Curtis and Gurling, 1991] remains highly desirable. However, even though the logistic regression model for the differences observed here does provide some discrimination between UP relatives of BPs and UP relatives of controls, it would not be appropriate to pilot it in a linkage study. Especially because the findings do not conform to expectations, they might well represent a process of optimizing on systematic differences between sites, or on chance differences between groups.

Thus, the task remains to develop a method to estimate a "caseness" index that accurately reflects the underlying reality, a reality that needs to be specified all the more clearly if we are to explore more complex genetic models such as oligogenic inheritance, parent-of-origin effects [McMahon et al., 1995], and anticipation [Gelernter, 1995]. It may be possible to tease out indicators of underlying bipolarity more proximal to the genotype based on psychological testing or clinical judgment in a sample collected expressly for this purpose. In the meantime, the indicators of bipolarity in unipolar relatives of bipolars remain important, but elusive.

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